Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C

[illegible] Harbourton Road
PO Box 200 Titusville, NJ 08560

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

FDA Docket No. 2004D-0187, 2004D-0188, and 2004D-0189
Three Draft Guidances for Industry entitled Premarketing Risk Assessment; Development & Use of Risk Minimization Action Plans; and Good Pharmacovigilance Practices & Pharmacoepidemiologic Assessment

Dear Sir/Madam:

As a leader in the discovery, development, manufacture and marketing of prescription medicines, Johnson & Johnson pharmaceutical business and research organizations are committed to improving health and well being through innovative products and services. We share the Agency's goal of bringing safer and more effective drugs to the market as rapidly as possible. We embrace the importance of risk management, and are pleased to have the opportunity to comment on the FDA's Draft Guidance of May 5, 2004, entitled, "Premarketing Risk Assessment, Development & Use of Risk Minimization Action, and Good Pharmacovigilance Practices & Pharmacoepidemiologic Assessment." I am sending these comments on behalf of the Johnson and Johnson pharmaceutical business and research organizations.

We agree with FDA that the ultimate goal of risk management is to ensure that efforts and costs involved in risk management efforts are expended on effective processes that achieve a positive benefit/risk balance for patients. With proper use, drugs can provide enormous benefit to patients and can reduce overall healthcare costs.

We have several broad comments to make about the overall risk management concept. This general feedback is found below. More specific comments as they pertain to each draft guidance can be found in the subsequent *attachments*.

- While the proposed guidances acknowledge that even large clinical development programs cannot reasonably be expected to identify all risks associated with a product, J&J is concerned that the FDA may attempt to require large numbers of additional studies to identify as many risks as possible prior to approval. Such an approach may result in significant delays in drug development.

- Consistent standards must be used across all Divisions so that decisions about individual drug products are not made on different criteria based on a particular reviewer's views. We

2004D-0188

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recommend that a high level review committee within the FDA be constituted to ensure that decisions regarding risk management that affect drug development programs and the need for RiskMAPs are made appropriately and consistently.

- Our hope is that any assessment and decision about risk management interventions would be based on the benefits as well as the demonstrated risk profile of the drug product. We believe that risk management programs/ interventions should balance access of patients to needed drugs with the level of concern. We were very pleased to see reference to the balancing of benefit to risk throughout the documents and also an acknowledgement that risk minimization plans should be used judiciously so as not to interfere with the delivery of benefit to the patient.

- We were also pleased to see that for most products, the FDA feels that routine risk minimization measures are sufficient. While that was stated in the original concept papers, it was made very clear in the proposed guidances that requirements for Risk MAPs will be the exception rather than the rule at the FDA and we agree with that approach.

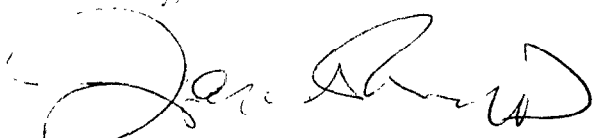
- Collaboration between the FDA and industry on the development and approval of RiskMAPs and pharmacovigilance plans is critical. We were pleased to see that the FDA recommends many interactions with industry to discuss safety as drug development proceeds. Again, it will be critical for the FDA to ensure that safety issues are evaluated as consistently as possible across Divisions and that there is a great deal of oversight regarding the decisions to require additional studies or a RiskMAP and the selection of tools which must be employed.

- Clearly, there are a number of stakeholders who must also collaborate with FDA and industry, including academic institutions, healthcare providers, third party payers, pharmacists, professional societies, and patient groups, if significant improvement in overall benefit/risk balance for patients is to be achieved. It was very welcome to see the FDA embrace this concept across the proposed guidances.

- Finally, Johnson & Johnson applauds the FDA's efforts to conform to harmonized international definitions and standards as much as possible. It is very difficult for industry to develop drugs efficiently if the health authorities use different approaches, definitions and standards.

In closing, we appreciate the opportunity to comment on these important draft guidances and look forward to working with FDA to ensure the safe and effective use of all prescription drug products.

Sincerely,



Janice K. Bush, M.D., Vice President
Liaison, Quality Management and Business Support
Johnson & Johnson Pharmaceutical Research & Development
Benefit-Risk Management

Attachments **(#3)**

Attachment II

Development and Use of Risk Minimization Action Plans Proposed Guidance

General Comments:

We were pleased to see that the FDA makes it very clear in the proposed guidance that for most products, routine risk minimization measures are sufficient to minimize risk and preserve benefits and that for only a small number of products should a RiskMAP be considered. J&J agrees that an appropriate PI along with good post marketing surveillance should be, in essence, the risk minimization measures for the majority of drugs. Since this is a primary tenet of the proposed guidances, we believe this should be reinforced at the Office level by measuring the number of products that require RiskMAPs and providing statistics on a yearly basis to industry.

Details should be provided about how the FDA plans to ensure that products in the same/similar class with similar safety profiles meet risk minimization expectations in a uniform matter. While it is very helpful to see that generics have been addressed as likely needing a RiskMAP if the innovator product has one (although it is difficult to understand why this requirement would not be an absolute if the product is actually a generic version of the same drug), how similar drugs for the same disease state would be handled still needs to be clarified.

Previously, it was suggested that the FDA include a complete review of all current and past RMPs so as to demonstrate the value of these overall programs as well as the individual tools used to achieve the objectives. We appreciate that the FDA is proposing to maintain a RiskMAP Web site, but it appears that the information will be primarily those data that it receives from sponsors and others. J&J would like to see an analysis by the FDA of previous plans and the tools used, including overall feasibility assessments. We understand there could be confidentiality issues, but believe that such an analysis could be done and still retain appropriate confidentiality since a number of programs have been publicly discussed. In addition, information on tool effectiveness and evaluation data would be available, and in isolation/out of context from the analyses and primary data, potentially misleading.

There is more information in this proposed guidance regarding when a RiskMAP should be considered or would be required. However, there is the statement that the FDA may recommend that a sponsor consider a RiskMAP based on the "Agency's own interpretation of risk information." This approach is certainly in the FDA's purview, but is of concern in that consistent standards must be used across all review divisions so that individual reviewers don't use different criteria in requesting such plans. We believe this is important in order to provide an evidence-based rationale for RiskMAPs for every drug for which they will be required.

In previous comments it was expressed that care must be taken not to overburden the healthcare system by using too many resource-intensive tools in RMPs. It was welcome to see that the FDA is acknowledging the need to use RiskMAPs judiciously so that drug availability is not encumbered and that access to patient benefit is not interfered with.

Also in previous comments, the collaboration needed between industry and FDA was called for. It is gratifying to see the attention paid to the various ways in which industry and FDA will have the opportunity to discuss safety issues early on in the drug development process, specifically at End of Phase II meetings or at specific meetings to discuss potential RiskMAP issues.

As stated earlier, J&J is very supportive of FDA's efforts to conform to harmonized international definitions and standards as much as possible. We think this is an opportunity for FDA to harmonize these proposed guidances with the ICH E2E draft Pharmacovigilance Planning document. Can there be some discussion of how these FDA documents relate to the ICH document, and special attention be paid to harmonizing definitions and terminology where possible?

Will these RiskMAPs be negotiated during NDA review and included in approval documentation? Would they be considered Phase IV commitments? It is imperative that the guidance outlines a process prior to approval (during NDA review) or prior to NDA submission to properly discuss and obtain consensus with the FDA on the RiskMAP so as not to impact the review and approval timelines or launch of a product.

FDA's general encouragement of early and open discussion of safety concerns may not be enough if there is not enough definition attached to the potential discussion opportunities.

Specific Comments:

Lines 171-177

Though it is laudable to set ideal goals, it is not realistic to achieve them absolutely. It is more appropriate to set high, but realistic and achievable, goals. To achieve absolute goals will probably require draconian risk minimization action plans that limit access of patients to medicines that they need, and may deter physicians from prescribing or recommending them if they perceive the burden on them or their patients as being excessive. Risk *Minimization* Plan, as indicated by the name, should be a realistic plan to minimize risk rather than to eliminate all risks. We agree with the FDA that the goals are translated into *pragmatic*, specific and measurable program objectives.

Lines 208-217

It is suggested "nature and rate of known risks versus benefits" be considered when trying to determine if development of a RiskMAP is desirable. The need to compare benefits to risks is obvious, although we agree with the FDA that such an assessment is a very complicated process. To avoid bias in how the risks are weighted in light of benefits, it might be useful for the FDA to consider models as they make such assessments in the future. Currently, this benefit-risk assessment is basically a judgment call, and that is partially due to the fact that most models are not sophisticated enough to be useful or have not been validated. While that is still the case, more work is being done with respect to evaluating such models as the Multi-Criteria Decision Analysis technique. Exploring and using such models as these might be considered as a way to help bring consistent thinking into the FDA review process concerning the balance of risks and benefits for drug products throughout the life cycle. A more rigorous approach may help to ensure that the assessment is not influenced, for example, by an inordinate emphasis placed on a very rare risk or on merely theoretical risks and that the assessment is actually more balanced.

According to the proposed guidelines, one of the characteristics to be weighed when determining RiskMAP desirability is the "existence of treatment alternatives". We suggest that this consideration include "and the benefit-risk balance of the treatment alternative".

Lines 226-228

It is not clear why opiates are taken as an example of products requiring specific RiskMAPs as the special controls in their distribution are already intended to ensure that.

Lines 258-343:

The previous concept paper on this topic had called for categorizing RMPs into levels. We were not in favor of this for many reasons and so we were happy to see that the FDA has rethought this position. Instead there is a description of categories of RiskMAP tools, which seems to be a more appropriate approach. We were also pleased to see that the proposed guidance notes that a selection of specific tools should not be used in an assessment of comparative safety to another drug product. However, we do note that the sentence in lines 263-265 is poorly worded, and we may have misunderstood its meaning. We suggest this be reworded to be clearer as to its meaning.

Lines 274-285

We acknowledge the need for direct information dissemination to healthcare practitioners may be part of a RiskMAP. Please clarify if the use of such health care practitioner letters would always fall under 21 CFR 200.5, including unique envelope requirements and red box (Warning)? For example, would communication/education to health care professionals describing a unique packaging/dosepack usage to reduce medication errors require a "Dear Healthcare Professional letter" with accompanying bells and whistles? Will all such communications/tools (education/outreach) require pre-approval?

Attachment II

Lines 356-366

Please elaborate on the mechanism for FDA's recommendation of class tools/labeling/text?

Lines406-407:

The proposed guidance states that the design of the RiskMAP should seek to avoid unintended consequences of tool implementation that obstruct risk minimization and product benefit. J&J absolutely agrees with the point, but we would like to see more from the FDA on how they propose to make sure that this does not happen. One of the most obvious ways that this occurs is when an inappropriately onerous RiskMAP drives doctors and patients to use a riskier drug without a RiskMAP. As stated above, this scenario has not been adequately addressed in the proposed guidance.

Lines 414-421

Is the FDA implying that industry must consider off label use and devise a RiskMAP taking this into consideration to minimize its possible safety consequences?

Lines 468-471

We suggest that these lines be deleted. They imply that statistical considerations are irrelevant or only marginally relevant to decisions about the need for a RiskMAP and its evaluation. This is obviously not the case, unless the FDA is really trying to assert that counter-measures should be implemented to address random variations in the observed data.

Lines 516-518:

Spontaneous AE data are described as "potentially" biased outcome measures. We suggest that this be corrected to say that spontaneous report data are "inherently biased outcome measures".

Lines 568-571

The proposed guidance discusses the potential for an evaluation of a RiskMAP to allow the opportunity to discontinue a tool if the individual tool is performing poorly. While poorly performing tools should be discontinued, we would also like to see the acknowledgement that it might be appropriate to discontinue a tool if it proved to be successful and therefore was no longer needed or if there were another redundant tool, which superceded the need for the tool.

Lines 581-588

Please clarify what degree of pretesting risk minimization tools will be required and what the process will be for identifying this need. Also clarity is needed as to whether the evaluation and testing of the tools is required to be submitted at the time of NDA submission or whether a plan to perform these activities before implementation would suffice.

In general, we believe that pretesting of assessment tools will be difficult, especially for new concepts. This may not be a realistic expectation for gathering meaningful information.

The proposed guidance suggests that if risks are identified in Phase 1 or 2, that Phase 3 trials could provide an opportunity to pretest targeted education and outreach tools. It would be helpful to have an example here. As we are developing a drug, if a significant risk is seen in Phase 1, it is unlikely that this drug would be continued in further development. If it is seen at the end of Phase 2, after proof of concept, this may be a more likely candidate.

Lines 632-637

Developing a complete risk minimization plan at an early stage (IND/NDA) can be difficult or impossible prior to approval of a product or agreed upon indications/settings for the treatment, as these things will greatly influence the use of the product and therefore the boundaries of the risk minimization plan.

Attachment II

Lines 666-674

Are RiskMAPs to be specific to a product or could they be unique to an indication? For example, if a product were under consideration for multiple indications, across divisions, but the risk were unique to one population under study, could the RiskMAP be assigned to this IND only?

Lines 823-824

Inclusion of raw data in the RiskMAP Progress Reports could be quite onerous without being worthwhile. It should be adequate for the sponsor to summarize the results and conclusions based on data collected.

Lines 838-839

And along similar lines, the proposed guidance states that a sponsor might choose to propose modifications to the RiskMAP "if the RiskMAP goals were not achieved". We would like to see some discussion about when it might be possible to modify a RiskMAP if the goals WERE achieved. In other words, will a RiskMAP be a never-ending activity or will there be the potential for modification or termination based on success?

In addition, this type of follow-up is difficult and can remain open-ended. At some point, the sponsor needs to be able to record the attempts made for follow-up and close the inquiry.

Also, this implies that all serious AEs would be followed until they are fully and permanently resolved. Would stabilization of the case be sufficient, if complete resolution is not anticipated?

Finally, does the FDA recommend any retrieved drop-out data evaluation/analysis?

Lines 878-881

FDA is asking for follow-up for late safety events, so some guidance on follow-up would be helpful.

This recommendation for follow-up should also be rephrased to, for example, 'after the end of the study drug administration' as data collection cannot continue beyond the period the subject has given informed consent for. Follow-up should be included in the informed consent (formal study).

Lines 897-899

It is recommended that AEs that are common to the class should be fully characterized in the NDA's ISS. How about AEs that are not common to the other members of the class? Wouldn't that be of even more interest?

Lines 920-925

The proposed guidance is requesting that hospital and other medical reports be submitted with the CRFs for patients who died or discontinued a study prematurely due to an AE. For some clinical trials, deaths and discontinuations due to AEs occur frequently, such as in a prevention trial in an elderly population that last for more than one year. Including hospital records for all of these cases would result in a significant increase in paperwork that should be carefully considered. Such submission of hospital records has not previously been required and may be difficult in light of recent HIPAA privacy regulation.

There must be allowance for data from countries where these documents cannot be obtained due to local data protection laws. We suggest that the FDA adds the clause "to the extent possible" and that it should also be specified that copies of the source document is acceptable, since the sponsor is most often not the owner of these documents.

Attachment I

Lines 402-559

The recommendations in this section are broad and could result in a huge increase in study requirements for individual drugs. We suggest that requests for such studies be based on specific risks and clear areas of public health concern. In addition, it should be clear that such data would be critical to be able to make better decisions about patient safety.

We note that the FDA begins this section by stating that some risk assessment issues would apply only in certain circumstances (lines 402-404), however the topics within the section are all given very general titles (Risk Assessment During Product Development and Safety Aspects that Should be Addressed During Product Development) which do not seem to be describing requirements which would only apply in certain circumstances.

There are always resources to consider when drug development programs are planned. The costs of any new requirements must be weighed carefully against potential benefits. If the recommendations increase the number or complexity of studies required, this could significantly increase the cost of drug development.

Lines 519-559

J&J is concerned that the proposed guidance states that all drug development programs should include assessments for QTc prolongation, liver toxicity, drug-drug interactions, polymorphic metabolism, as well as two new additions, nephrotoxicity and bone marrow toxicity. It is somewhat reassuring that the proposed guidance states that addressing these would not always involve the generation of data, but it is not explained when preclinical studies or other data could be appropriate. Once again, we recommend that there be a discussion about these potential issues during drug development, but that there not be an absolute requirement for such assessments.

Lines 581-583

We believe the request that the sponsor use one coding convention or dictionary throughout a clinical program is not realistic in view of the long duration of some study programs. Also it should be clarified whether this extends to proposing use of one version of a dictionary or whether the intent is only to advise against switching from, e.g., WHO-ART to MedDRA, halfway through a program unless unavoidable.

Lines 662-664

Examples from FDA of grouping approaches using MedDRA would be helpful for industry.

Lines 685-686

We recommend that you insert the statement "Study of the temporal association is in particular worth exploring for those adverse events where the temporal relationship between product exposure and ensuing adverse event is well understood."

Lines 858-870

It would be a violation of the principle of informed consent to try to obtain information from subjects once they have withdrawn consent. This should at least be rephrased to something like 'subjects considering withdrawing consent should be encouraged to provide the reason and encouraged to continue to provide information if related to a serious or significant safety issue'.

Attachment I

Lines 338-340

Will the FDA provide guidance to industry as to which population groups they want to see reflected in the demographic relationships (beyond gender, age and race) since that will affect collection forms and database data fields?

Lines 345-346

Since there are a number of dietary supplements that are readily available to consumers, it is difficult to know which ones are "commonly used". Use of some products may be culture or geographically dependent.

Lines 363-366

Is this for biomarkers which are well established and validated for use as biomarkers in the clinic? The proposed guidance should clarify this point or expand this section to discuss the appropriateness of using novel biomarkers which may not be fully proven.

Lines 419-421

How will sponsor/product premarketing assessments be reflected in RiskMAPs if tools are used during clinical development programs? For example, if tools (including screening, prescriber education) are used proactively in development programs, and no signal is detected, will the tools be included in product labeling?

Lines 423-424

The proposed guidance states, "for drugs with likely CNS effects, sponsors should conduct assessments of cognitive function, motor skills, sexual function and mood". We believe this is too broad. Allowances need to be made for well-characterized compounds with known CNS effects. It would be overly onerous to require sponsors developing new dosage forms of old drugs to be held to all of these requirements.

Lines 443-449

The advice regarding the use of large simple trials is welcome. However, we would like to ask the FDA to clarify how to reconcile the reporting of a single study endpoint (rather than all serious adverse events) with current European recommendations. J&J has found this point to be an area of difficulty in some of our recent work.

Also, the FDA should spell out careful criteria as to when such a LSSS would be needed, since such trials can easily become complex and very resource intensive.

Lines 473-491

The guidance is requesting an extensive premarketing risk assessment regarding possible medication errors. It is not clear if this is a request for development programs generally or if this would be only for certain circumstances or types of products. Potential medication errors were discussed in detail in the industry comments to the FDA regarding the "Tome". There is still an issue with definition since currently we only have adverse event definitions for specific patients and events, not hypothetical situations such as confusion over drug names. Our additional comments are that certainly the FDA should not be attempting to effect changes in existing regulatory standards via guidances.

Attachment I

Lines 175-184

Does the "size of database for chronic use" apply to all chronic drugs, not just those which are novel in mechanism or class (1500)? Does this mean 1500 exposed at multiple dosing (with no limit on exposure)?

Lines 181-184

This text is very subjective and not consistent with ICH E1 guidance. The interpretation of "reasonable representation" may differ vastly among reviewing divisions at the FDA.

Lines 191-201

It is stated that databases larger than 1500 may be appropriate if there is concern about last developing adverse events. Wouldn't this more appropriately be addressed with smaller databases and longer exposures?

The FDA states that larger than 1500 patients may be needed if warranted based upon data from animal studies. An example of such would be useful as preclinical results are not always predictive of human experience.

With regard to the animal data, does this mean any data from animal studies or does it mean data from long-term animal studies? An example would help to clarify.

Lines 215-218

Depending on the safety issue at hand, this request clearly refers to sizing trials based on safety and efficacy. For detecting events that are less than likely, this will amount to very large trial sizes that might prove prohibitive for sponsors.

Lines 240-243

The proposed guidance states that one of the principles which should be used in developing a premarketing database is that "terminology, assessment methods, and use of standard terms" should be examined. Can the FDA assure industry that MedDRA will continue to be the dictionary for standard terminology?

Lines 252-257

We believe that execution of long-term controlled studies is not practical, especially placebo-controlled studies. We suggest that this is an unrealistic expectation.

Lines 284-285

We question the wisdom of the approach that only patients with obvious contraindications be excluded from study entry in Phase 3 trials. If a sponsor is studying a certain class of drug and is already aware of certain warnings and precautions that should apply in addition to contraindications and is willing to accept the resultant labeling, why would a sponsor unnecessarily expose these types of subjects in Phase 3 trials?

Attachment I

Pre-Marketing Risk Assessment Proposed Guidance

General:

Overall, this proposed guidance describes many possible safety assessments, which might be done during drug development. While we are pleased that the FDA states that many recommendations in the guidance are not intended for all products, we do have concerns about the extent of information which may be requested on specific products.

The FDA has stated publicly that they will base decisions on data. We support that approach, but our concern is that increased amounts of data will be required prior to approval, which will result in delays in drug development and delays in getting needed medicines out to patients.

Specific Comments:

Lines 64-67

Please provide examples of, or define, "unusual type or level of risk".

Lines 83-89

Please provide examples of consideration of stakeholder input (registries, ad boards) as well as suggested make-up of such boards.

Lines 137-141

This paragraph would benefit from an example. Preclinical data can flag up many *potential* problems, but experience-based judgments are made as to which are of most concern for clinical evaluation.

Also, is the FDA recommending any change in the submission format for safety data by a sponsor? How is the existing safety evaluation of a product different or deficient from a review standpoint? Should the approach of performing risk assessments on pivotal studies be formalized further (to become an integral part of the pre-NDA (and other such important discussions/meetings) and/or be adequately pre-specified? If so, how?

Lines 164-165

For products intended for short-term or acute use, the proposed guidance states it is difficult to offer general guidance on the appropriate target size of clinical safety databases. Our fear is that in the absence of general guidance on target size of clinical safety databases for acute use, with the only guidance available being for long-term or chronic use, there might be an effort to apply chronic standards to acute use products.

Lines 175-234

The proposed guidance references the ICH guidance E1A when describing some circumstances where a larger than normal safety database might be needed. This section still includes conditional and ambiguous language that could be broadly applied in a highly subjective or arbitrary manner. We are pleased that the FDA has stated that they are not suggesting that larger databases will be required or should be the norm. However, we are still concerned that increasing the size of the database above the usual requirements without specifically defining the concern or objective is not likely to significantly add to an assurance of patient safety. It will be critical for there to be consistency across Divisions and high-level oversight by Division Directors to ensure that requirements for larger databases are made appropriately.

Attachment III

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment Proposed Guidance

General Comments:

J&J agrees with the FDA that it is not possible to detect all safety concerns during clinical trials. Post approval safety data collection and risk assessment is vital to ensure that patients are able to take our drugs safely, and we are pleased to see that the FDA supports that for most products routine pharmacovigilance is sufficient for postmarketing risk assessment.

One of our main concerns with this proposed guidance is that the document suggests that data mining methods be used. No estimates of sensitivity or specificity of such methods are offered. For example, there are no estimates of the frequency with which such methods generate false positives or of the cost of pursuing them. Because all resources are limited, choices must be made among the various strategies available for risk reduction. Thus, such estimates (specificity, cost of false positives) are necessary for forming a rational decision about the use of data mining methods.

The concept paper on this topic was somewhat vague about the FDA's expectations regarding the difference between a "signal" that represents an investigative lead or alert and a "signal" that may require a Pharmacovigilance Plan or other specific action on the part of the sponsor. The proposed guidance still does not actually define what a "signal" is. There is an implied definition of an excess of AEs associated with a product, but then there is a whole list of "safety signals that warrant further investigation" (lines 361-384 in text) which are potentially more substantial than just a simple excess of events. However, the one place in the proposed guidance where the term signal is defined is in the Data Mining section where it is stated "a signal is operationally defined as any product-event combination with a score exceeding the specified threshold". To further add to the confusion, the FDA appears to envision a sequence of "signal to potential safety risk to safety risk". Since we will be asked to do quite a bit of investigation based on "signals" it seems appropriate to have a clear definition stated and to use it consistently throughout the final guidance.

Since both the ICH E2E document and the FDA guidances are in draft, we urge the FDA to ensure that terminology is harmonized among these documents; for example, currently the Pharmacovigilance Plan in the FDA draft guidances and the one in the ICH E2E document appear to have different attributes.

The guidance refers to "observational studies", "Pharmacoepidemiologic Safety Studies", "registries" and "surveys" with no clear definition of what these are and the difference among them. While we understand that the focus is on a higher broader view, it does not provide adequate guidance on individual case reports from all these sources, how often the company needs to search for valid cases and when is a case valid. What is the sponsor obligation in these activities? It would also be helpful if the "observational study", "registry", and "survey" definitions/usage were consistent with EU use of the term (volume 9).

Indeed, to some degree, this document is so "general" regarding theory and caveats of performing pharmacovigilance, that it might be better to present it as a "Points to Consider" document and not as "guidance".

Specific Comments:

Lines 145-149

While ideally, specially trained safety clinicians would best perform follow-up, this recommendation has significant resource implications for industry and has been addressed in the comments to the "Tome".

Lines 157-159

What is the definition of "aggressive follow-up"?

Attachment III

Lines 252-271

Although we agree that a series of cases may be evaluated regarding potential associations between an AE and drug exposure, there is no methodology that is reliable and reproducible for individual causality assessments. Therefore, we recommend that case level causality assessment should not be a requirement.

The proposed guidance includes the WHO terms for causality, yet does not recommend any specific categories for causality assessment. Since we do agree that causality assessments may be used for aggregate data, a recommendation from the FDA would be helpful in standardizing assessments.

Lines 316-317:

The sentence "Data mining is not the only technique used to make causal attributions between products and adverse events" should be deleted. Data mining is NOT a technique which can be used to make causal attributions, so such a sentence would be very misleading if it were to stay in the final guidance.

Lines 333-338

The various data mining methods are not compared. The document asserts that they yield similar results when the number of reported events exceeds 20. However the point of using data mining methods is early detection of signals, so performance differences among the various data mining methods on small numbers of reports may be critical.

Lines 347-349:

We were pleased to see that the FDA regards "signals" generated by data mining as hypothesis-generating only.

Line 375:

FDA seems to be inserting the idea of "potential" medication errors into this guidance document as a consideration of a "safety signal that may warrant further investigation". This is not an accepted term, nor is this the appropriate place to attempt to effect changes in existing regulatory standards.

Lines 388-416

The document appears to prefer risk (events per person exposed) to rate (events per person time exposed) as the measure of event frequencies. For many drugs, e.g. anti-hypertensives, benefits are proportional to person time exposed to the medication, not to persons using the medication, and for such medications, adverse event rate (rather than risk) appears to provide the preferable comparison to benefit.

Lines 425-431

In addition, the likelihood of observing an event unrelated to the medication (a baseline event) is more closely related to the person time of exposure than to the number of persons exposed, and data on person time exposed are more widely available and likely to be more reliable than data on people exposed, so again, rate appears to be the FDA's preferable measure. Finally this proposed guidance specifically suggests the use of rates rather than risks (later on in lines 696-702 and 825-826). Greater clarity on rates vs. risks would be helpful.

Lines 491-493

We suggest that the sentence should read "relative risk *to* exposed patients" instead of "relative risk *of* exposed patients".

Attachment III

Lines 511-513

The advice to conduct multiple studies on the same question appears to ignore the issue of resource limitations.

Lines 553-556

Although all three of these guidance documents indicate that the protection of patient privacy is critical, no evidence is offered that there are real problems in this arena. The advice on the importance of confirming diagnoses suggests different and more permissive policies for access to patient data, e.g. access to medical charts, from the policies suggested by the advice that protection of patient privacy is critical. Thus, it would be useful to clarify the policy issues raised by the apparent tension between these two laudable objectives (privacy and complete data).

Lines 636-642

It would be helpful if the FDA would expand on what is meant by "further study". To what extent is this a strong recommendation rather than a suggestion?

Also, can the FDA comment on using equivocal data from preclinical studies as weight of evidence?

Lines 644-646

This sentence should be rewritten. As written now, it says: "When a safety signal is identified that may represent a potential safety risk, the FDA recommends..." Our issue is that with *may* and *potential* and *risk* all strung together, one is so far from an actual event that there seems to be no minimum for the recommendation. Anything could qualify!

Lines 700-735

When implementing a Pharmacovigilance Plan, either initiated by the sponsor or at the request of the FDA, is it expected that Evaluation Plans and timeframes be in place at the start? If not, when should the sponsor address the Evaluation Plan with the FDA? And when should the evaluations occur? Annually? Bi-annually? How are the Pharmacovigilance Plans/RiskMAPs to be coordinated across divisions, especially when a marketed product is under evaluation in a second division?

Lines 739- 742

It is stated that pharmacovigilance plans may be appropriate for products which have "safety signals" identified pre- or post-approval. Again, the use of the term signal is confusing here and perhaps you mean to use the term " safety risk" instead of "safety signal".

Lines 756-761

Please include a definition of "active surveillance".